REMARKS

Applicant respectfully requests reconsideration. Claims 16-22 were previously pending in this application. Claims 16-22 have been amended. As discussed below, the amendments to these claims is supported by the specification. Claims 23-29 were previously cancelled. New claims 30-44 have been added. As a result, claims 16-22 and 30-44 are pending for examination with claim 16 and 33 being independent claims. No new matter has been added. See page 11, lines 11-15; page 18, lines 7-11; and page 19, Table 1 and lines 20-22 for support for new claim 30. New claims 31-32 are based on former claim 17. See page 23, lines 20-34 for support for new claims 33-34. See page 24, lines 9-15 for support for new claims 35-37. See page 25, lines 12-15 for support for new claim 38. See page 18, lines 4-11 for support for claims 39-40. See page 25, lines 15-36 for support for new claims 42-44.

In addition, claims 16-18 and 21-22 have been amended to specify the extracellular matrix composition comprises collagen. The application supports these amendments at, inter alia, (Page 5, lines 13-23; page 18, lines 4-23; and Table I). As disclosed in the specification, the instant invention is designed to "overcome the shortcomings of bovine injectable collagen and other injectable materials" for soft tissue augmentation (Page 5, lines 26-30). Those shortcomings relate to the antigenicity of bovine collagen in humans (Page 4, line 35 to page 5 line 23). The shortcomings were so intractable that rather than injecting xenogeneic collagen, biocompatible ceramic matrices were attempted (Page 5, lines 13-23).

The instant invention overcomes these shortcomings with two related injectable compositions: 1) "naturally secreted extracellular matrix preparations" themselves, and 2) "preparations derived from naturally secreted extracellular matrix" (Page 5, lines 32-34, emphasis added). In the former, extracellular matrix preparations are obtained from living human tissue grown *in vitro*, and contain a mixture of extracellular matrix components for example, collagen type I, collagen type III, and collagen type IV (Page 18, lines 4-11; page 26, lines 22-25; page 30, lines 22-23; and Table I). Whereas in the latter, the extracellular matrix preparations serve as a source of specific naturally secreted human matrix components. For example, preparations of specific collagen proteins are "derived" (Page 31, lines 27-30, emphasis

added) or "isolated" from the extracellular matrix preparations (Page 9, lines 3-6 and page 32, lines 17-22, emphasis added).

In one example of the present invention, naturally secreted collagen derived from human dermal tissue produced *in vitro* is structurally equivalent to collagen derived from a normal adult human dermal tissue sample (Page 31, line 25 to page 32, line 22). Injectable collagen preparations were isolated from naturally secreted human extracellular matrix produced *in vitro* (Figure 2A-D and page 9, lines 3-6) and are useful for the treatment of skin and tissue defects (Page 23, line 20 to page 26, line 11). Using other processes disclosed in the invention, injectable compositions containing different proportions of the various types of collagen (e.g., Collagen Type I, III, and IV) can be isolated (Page 18, lines 4-23 and Table I). Thus, the invention discloses preparations derived from naturally secreted extracellular matrix, and particularly collagen preparations, that are useful as injectable compositions for repairing skin or tissue defects (Page 1, lines 10-17 and lines 34-35).

Double Patenting Rejection

The Examiner provisionally rejected claims 16-22 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-59 of copending Application No. 10/851,773; and rejected claims 16-22 on the ground of nonstatutory obviousness-type double patenting over claims 1-16 of U.S. Patent No. 6,284,284 B1 or claims 1-10 of U.S. Patent No. 5,830,708.

Applicant traverses the rejections but notes that, upon an indication of otherwise allowable claims, a terminal disclaimer will obviate the rejections.

Rejections under 35 U.S.C. §112

The Examiner rejected claims 16-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner argues that in line 2 of claim 16 "naturally secreted extracellular matrix" is uncertain as to meaning and scope, and that being natural and secreted is relative and subjective. As the Examiner is aware, the meaning of a particular claim term may be defined according to

the usage of the term in the context of the specification (See MPEP 2111.01-IV). Thus, the meaning of the claim terms "naturally" and "secreted" can be found in the specification at least on page 7, lines 10-13. Accordingly, withdrawal of this rejection of claim 16 under 35 U.S.C. §112, second paragraph for indefiniteness is respectfully requested.

The Examiner indicates that claim 17 is unclear as to the step that produces the composition of claim 16. In the interest of expediting prosecution, Applicant has amended the claim to read "is produced by a method comprising". Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner argues that claims 19 and 20 are unclear by failing to have an antecedent basis for "the framework" (Claim 19), and "the three-dimensional framework" (Claim 20), and that Claim 16 on which those claims depend does not require a framework. Applicant has amended claims 19 and 20 to be dependent on Claim 17, which requires a three-dimensional framework and provides antecedent basis for "the framework" (Claim 19), and "the three-dimensional framework" (Claim 20). Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §102

The Examiner rejected claim 16 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 5,656,478 (Tanagho et al.). Applicant traverses this rejection.

The Examiner indicates that Tanagho et al. (U.S. Patent No. 5,656,478) discloses a composition containing smooth muscle cells, extracellular matrix, and a pharmaceutically acceptable carrier, and that the extracellular matrix (Matrigel™) is inherently human naturally secreted since it is obtained from human tissue. Applicant respectfully traverses the rejection. Matrigel™ is a commercially available basement membrane composition obtained from Engelbreth-Holm-Swarm mouse sarcoma cells (see Appendix: Matrigel™ product specification sheet from BD Biosciences, Bedford, MA). Thus, it is not inherently human naturally secreted, and does not anticipate the instant claims.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 16-22 under 35 U.S.C. §103(a) as being unpatentable over Tanagho et al. in view of U.S. Patent No. 5,032,508 (Naughton et al.) and in further view of U.S. Patent No. 5,460,939 (Hansbrough et al.) or U.S. Patent No. 5,478,739 (Slivka et al.). Applicant traverses this rejection.

A *prima facie* case of obviousness must demonstrate that the combined references teach or suggest all of the instant claim limitations (MPEP 2143). None of the cited references teach steps to isolate a naturally secreted human extracellular matrix comprising killing cells and removing dead cells and cellular debris as disclosed in the instant invention. Thus, the combination of these references does not teach or suggest all of the instant claim limitations. In this regard, the Examiner indicates that it would have been obvious to kill the cells prior to implantation. However, in light of the fact that each of the cited references discloses implantation of living cells, killing cells changes the basic principle under which any them were designed to operate and, therefore, precludes a *prima facie* case of obviousness (MPEP 2143.01 VI).

Also, as shown above, the Matrigel™ of Tanagho et al. is a murine composition, not a human composition. In light of the known problems with antigenic responses to bovine collagen, a murine teaching would not be relied upon by one of ordinary skill in the art.

Moreover, Applicant has not found any disclosures in Hansborough et al. or Slivka et al. that teach culturing cells on a framework to secrete extracellular matrix. Applicants respectfully request that the Examiner identify its location in a subsequent Office Action if the rejection is not withdrawn. *See* 37 C.F.R. § 1.104(c)(2) (" the particular part relied on must be designated as nearly as practicable").

Finally, Tanagho et al. teaches the use of smooth muscle cells combined with commercially available basement membrane (Matrigel™) to promote smooth muscle tissue growth *in vivo*. Tanagho et al. teaches that Matrigel alone has no effect on smooth muscle tissue growth *in vivo* (Column 8, Table A). Thus, Tanagho et al. teaches away from the instant claimed invention. One skilled in the art could not derive any reasonable expectation of success based on Tanagho et al., as is required for a *prima facie* obviousness case (MPEP 2143.02), that an injectable naturally derived human extracellular matrix would be useful in repairing tissue

defects. Consequently, one skilled in the art would not have been motivated to look beyond Tanagho et al. and combine the aforementioned references to produce the instant invention.

Based upon the foregoing arguments, withdrawal of this rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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